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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/970,382	10/03/2001	Su-Chun Zhang	960296.98211	9657

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EXAMINER
NGUYEN, QUANG

ART UNIT	PAPER NUMBER
1636	6

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/970,382	Applicant(s) ZHANG ET AL.	
	Examiner Quang Nguyen	Art Unit 1636	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-17 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-17 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-17 are pending in the present application, and they are examined on the merits herein.

Drawings

Color photographs require materials not yet submitted by Applicants. Color photographs and color drawings are acceptable only for examination purposes unless a petition filed under 37 CFR 1.84(a)(2) is granted permitting their use as acceptable drawings. In the event that applicant wishes to use the drawings currently on file as acceptable drawings, a petition must be filed for acceptance of the color photographs or color drawings as acceptable drawings. Any such petition must be accompanied by the appropriate fee set forth in 37 CFR 1.17(h), three sets of color drawings or color photographs, as appropriate, and an amendment to the first paragraph of the brief description of the drawings section of the specification which states:

> The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the U.S. Patent and Trademark Office upon request and payment of the necessary fee.

Color photographs will be accepted if the conditions for accepting color drawings have been satisfied.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c). (See change of mailing adderess for the First Inventor Su-Chun Zhang).

Claim Objections

Claim 12 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. This is because the step (c) of the dependent claim 12 does not further limit the step of culturing embryoid bodies of the method in claim 1, from which claim 12 is dependent upon.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-11 and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 3-11 and 13 recite the limitation "the embryoid bodies" in line 5 of claim 1. There is insufficient antecedent basis for this limitation in the claim. In previous steps (a) to (b) of the method in claim 1, there is no recitation of embryoid bodies. Moreover, there is no connection between step (c) which is culturing embryoid bodies

and the steps of obtaining a primate embryonic stem cell culture and propagating the stem cells.

Claims 4 and 13 recites the limitation "step (d)" in line 2 and line 1 of the respective claims. There is insufficient antecedent basis for this limitation in the claim. There is no step (d) in the method recited in claim 1, from which both claims 4 and 13 are dependent upon.

In claim 3, it is unclear what is encompassed by the phrase "differential enzymatic treatment and adhesion". The enzymatic treatment and adhesion are differential in which manner and between which cell populations in the claimed method. The metes and bounds of the claim can not be clearly determined.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 14-17 are rejected under 35 U.S.C. 102(e) as being anticipated by Luskin (U.S. 6,251,669) as evidenced by Sandberg et al. (US2002/0028510A1).

The claims are drawn to an isolated cell population comprising at least 72% neural precursor cells; the same wherein the population comprises at least 84% or at least 90% or at least 95% neural precursor cells.

Luskin discloses an isolated cellular composition comprising at least 95% neuronal progenitor cells which express a neuron-specific marker (e.g., Class III β-tubulin, MAP2 and others) and which can give rise to progeny which can differentiate into neuronal cells (see col. 5). Sandberg et al. (US2002/0028510A1) teach that neural precursor cells are stem and/or progenitor cells which will differentiate into or become neural cells or cells which will ultimately exhibit neuronal or glial markers (page 5, col. 2, last paragraph), and that the terms "neural cells" and "neuronal cells" are generally used interchangeably, and neural/neuronal phenotypic markers include Musashi-1, Nestin, Class III β-tubulin, MAP2 and others (page 6, col. 1, top of the first paragraph). Absent evidence to the contrary, the isolated cellular composition disclosed by Luskin is indistinguishable from the isolated cell population of the presently claimed invention.

Accordingly, Luskin anticipates the instant claims.

Claims 1-2, 4-6 and 10-16 are rejected under 35 U.S.C. 102(e) as being anticipated by Carpenter (WO 01/88104 with an international filing date of 5/16/01 with U.S. priority date to 5/17/2000; IDS).

Claims 1-2, 4-6 and 10-13 are drawn to a method of differentiating primate embryonic stem cells into neural precursor cells, comprising the steps of: (a) obtaining a primate embryonic stem cell culture, (b) propagating the stem cells, and (c) culturing

embryoid bodies formed from the propagated stem cells of step (b) in a medium containing an effective amount of fibroblast growth factor 2, wherein neural precursors are generated; the same method with various limitations recited in the dependent claims. Claims 14-16 are directed to an isolated cell population comprising at least 72% neural precursor cells; the same wherein the population comprises at least 84% or at least 90% neural precursor cells.

Carpenter discloses methods for culturing stem cell populations in a cocktail of growth conditions that initiates differentiation and establishes the neural progenitor population. Carpenter teaches that primate Pluripotent stem cells (pPS cells) including human, rhesus and marmoset embryonic stem cells of Thomson et al. as well as human embryonic germ cells of Shamblott et al. and other types of pluripotent cells are maintained either on irradiated primary mouse embryonic fibroblasts or in a feeder-free system, and expanded by serial passaging (pages 8-10, under "Sources of stem cells"; page 19, lines 13-22). Embryoid bodies (Ebs) are produced from the propagated human embryonic stem cells (e.g., hES cell lines used such as H1, H9, H13, H7NG) and they are cultured in non-adherent cell culture plates in a medium composed of 80% KO DMEM and 20% non-heat-inactivated FBS supplemented with 1% non-essential amino acids. After 4-8 days in suspension, Ebs are plated onto a substrate and allowed to differentiate into neural precursors in the presence of selected differentiation factors (page 19, lines 23-31). One of the disclosed set of conditions includes the incubation of Ebs onto fibronectin in DMEM/F12 with N2 and B27 supplemented with 10 ng/mL human EGF, **10ng/mL human bFGF**, 1 ng/mL human IGF-1, and 1 ng/mL human

PDGF-AA. After 2-3 days in these conditions, 25-66% of the cells express A2B5. This population is enriched by magnetic bead sorting to **48-93%** purity (example 2 and Table 4). Under another set of conditions, after culturing for about 2-3 days 25-72% of the cells express NCAM (example 1 and Table 3). Carpenter further teaches that upon plating out the embryoid bodies onto the substrate without dispersing the cells, neural cell precursors migrate out of the embryoid bodies and on to the extracellular matrix. Subsequent passaging of these cultures into an appropriate medium helps select out the neural progenitor cells (page 11, lines 34-38). Additionally, Carpenter discloses that neural stem cells can be cultured with a medium comprising glucose, transferrin, insulin, selenium, progesterone, and several other growth factors as taught in U.S. Patent No. 5,968,829 (page 8, lines 34-36). It is also noted that the referred medium also contains heparin and putrescine.

Accordingly, the teachings of Carpenter meet all the limitations of the instant claims. Therefore, Carpenter anticipates the instant claims.

Claims 1-17 are rejected under 35 U.S.C. 102(a) as being anticipated by Su-Chun Zhang et al. (Poster in Keystone Symposium on Pluripotent Stem Cells, 2/6/2001; IDS).

Su-Chun Zhang et al. disclose the same method for directed differentiation of human embryonic stem cells into neural precursors, and subsequent purification of the neural precursors as that of the presently claimed invention (see the entire article presented as a poster in the Keystone Symposium on Pluripotent Stem Cells). The

isolated cell population containing neural precursors from human ES cells would have the same characteristics (e.g., the percentage of neural precursor cells in an isolated cell population) as that of the presently claimed invention because it is prepared by the same method using the same materials.

Accordingly, Su-Chun Zhang et al. anticipate the instant claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 6-7 and 14-17 are rejected under 35 U.S.C. 103(c) as being unpatentable over Carpenter (WO 01/88104 with an international filing date of 5/16/01 with U.S. priority date to 5/17/2000; IDS).

Claims 1 and 6-7 are drawn to a method of differentiating primate embryonic stem cells into neural precursor cells as recited in claim 1, wherein the percentage of neural precursor cells in the culture step (c) is at least 84%. Claims 14-17 are directed to an isolated cell population comprising at least 72% neural precursor cells; the same wherein the population comprises at least 84% or at least 90% neural precursor cells.

Carpenter discloses methods for culturing stem cell populations in a cocktail of growth conditions that initiates differentiation and establishes the neural progenitor population. Carpenter teaches that primate Pluripotent stem cells (pPS cells) including human, rhesus and marmoset embryonic stem cells of Thomson et al. as well as human embryonic germ cells of Shamblott et al. and other types of pluripotent cells are maintained either on irradiated primary mouse embryonic fibroblasts or in a feeder-free system, and expanded by serial passaging (pages 8-10, under "Sources of stem cells"; page 19, lines 13-22). Embryoid bodies (Ebs) are produced from the propagated human embryonic stem cells (e.g., hES cell lines used such as H1, H9, H13, H7NG) and they are cultured in non-adherent cell culture plates in a medium composed of 80% KO DMEM and 20% non-heat-inactivated FBS supplemented with 1% non-essential amino acids. After 4-8 days in suspension, Ebs are plated onto a substrate and allowed to differentiate into neural precursors in the presence of selected differentiation factors (page 19, lines 23-31). One of the disclosed set of conditions includes the incubation of Ebs onto fibronectin in DMEM/F12 with N2 and B27 supplemented with 10 ng/mL human EGF, **10ng/mL human bFGF**, 1 ng/mL human IGF-1, and 1 ng/mL human PDGF-AA. After 2-3 days in these conditions, 25-66% of the cells express A2B5. This

population is enriched by magnetic bead sorting to **48-93%** purity (example 2 and Table 4). Under another set of conditions, after culturing for about 2-3 days 25-72% of the cells express NCAM (example 1 and Table 3). Carpenter does not specifically teach that at least 84% of the cells in the cultures of embryoid bodies with the presence of bFGF are neural precursors or an isolated cell population comprising at least 95% neural precursor cells.

However, it would have been obvious and within the scope of skills for an ordinary skilled artisan to obtain the same recited percentages of neural precursor cells that are differentiated from embryoid bodies using the method taught by Carpenter by incubating the Ebs in the presence of selected differentiation factors (e.g., bFGF among others) for a longer period of time. This is because Carpenter merely exemplified that 25-66% of the cells express A2B5 (indicating neural precursors) and 25-72% of the cells express NCAM (indicating neural precursors) after 2-3 days of incubation under differentiating conditions in the presence of bFGF, and that the percentage of differentiated neural precursors would be increased upon a prolonged culture under differentiating conditions. As such, an isolated cell population comprising at least 95% neural precursor cells would also be obtained via various means of further purification approaches taught by Carpenter.

Accordingly, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Dave Nguyen, may be reached at (703) 305-2024, or SPE, Irem Yucel, Ph.D., at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst, Tracey Johnson, whose telephone number is (703) 305-2982.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636.

Quang Nguyen, Ph.D.

REMY YUCEL, PH.D
SUPERVISORY PATENT EXAMINER
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